CHANGES IN THE HUMAN CENTRAL NERVOUS SYSTEM IN BOTULISM

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Death from food poisoning has long been known. About one hundred years ago it was ascribed to metallic poisons from kitchen utensils. In 1820, Kerner,[1] in describing a severe outbreak of food poisoning from eating smoked meat and sausage, was the first to apply the name "ptomaines" to the putrefactive poisons formed in organic substances; forty years later Trichinella spiralis was found contaminating food and shortly afterward the bacterial origin of food poisoning was announced by Gaertner, Gaffky and Paak and Achard and Bensaude.[2]

Of all the organisms found in food B. botulinus, through its toxin, is the most harmful for man and animal. It was first described by Van Ermengem,[3] who discovered it in a ham, the eating of which led to fifty deaths.

Since that time many contributions have been added to our knowledge of botulism, and it has been established that the bacillus botulinus is found not only in sausage, as its name implies, but also in other foods. Two deaths from drinking clam-juice have been reported;[4] three from eating salted herring;[5] three from cheese[6] and a great number from spoiled meat and vegetables.[7]

During the recent outbreak of food poisoning from canned olives in various parts of this country, especially in California, the clinical symptoms and morphology of the organism have again been described, and a few reports on the pathologic changes in the human body have been added.

The following report deals with the study of a brain-stem examined in serial sections from a case of botulism in a girl, 17 years old.

During Nov., 1919, 5 persons became sick in Sioux Rapids, Iowa, from eating smoked ham and salted pork, kept in a barrel. For the details and careful observation of the illness of all these I am greatly indebted to Dr. E. E. Munger of Spencer, Iowa. The meat was eaten in a farm-house close to the village and at least 2 of the 5 persons, one of whom died, were taken ill abruptly after leaving the farm-house where they had been stopping for a short time. Except for a nurse, these were all of one family; two—mother and daughter—died. Regarding the nature of the third death, that of the nurse,

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[1] Monograph, 1820.

[2] Cited by Hübener, Ergebn. d. inn. Med. u. Kinderh., 1912, 9, pp. 30-102.

[3] Ztschr. f. Hyg. u. Infectionskrankh., 1897, 26, p. 1; Arch. de pharmacodyn., 1897, 3, p. 204; Handbuch der pathog. Micro-organ, Kolle-Wassermann, 1912, 4, p. 909.

[4] Bine, R.: Boston Med. & Surg. Jour., 1917, p. 559.

[5] Bitter: Deutsch. med. Wchnschr., 1919, 45, p. 1300.

[6] Nevin: Jour. Infect. Dis., 1921, 28, p. 226.

[7] Schede: Med. Klin., 1916, 12, p. 1309. Dickson: Jour. Am. Vet. Med. Assn., 1917, 69, p. 966; Calif. State Jour. Med., 1916, 14, p. 143; Proc. Soc. Exper. Biol. and Med., 1916, 14, p. 47. McCaskey: Am. Jour. Med. Sc, 1919, 57, p. 158. Emerson and Collins: Jour. Lab. & Clin. Med., 1920, 5, p. 559.

brought from Sioux Falls, some doubt exists because she left this place on Nov. 8, became suddenly ill Nov. 15 while caring for another patient in South Dakota, and died 22 hours after the onset of the illness. One of the relatives, a sister-in-law, was only mildly ill for a few days. Nov. 5, she noticed that some of the pork given her was spoiled and threw it away. She had received the pork at the farm-house from the same barrel. Several others were ill at this time but with symptoms not definitely of botulism.

The illness of a fifth patient, a man, S. A., began Nov. 5 with a dry throat and mouth, dysphagia and restlessness; delirium became marked, and he talked for 5 hours at one time; he complained of headache, pain in the legs and back of the neck; there was a sighing respiration with distinct air hunger; blood pressure on Nov. 12 was 125 systolic and 85 diastolic. He improved gradually, and Dec. 25 had practically recovered.

The initial symptoms of the illness of the daughter, 17 years old, were great dryness of the mouth and throat; later she perspired freely, complained of sore throat, pain in the back of the neck and ringing in the ears. She became very restless and moaned and groaned constantly. There was edema of both sides of the face and neck. A bright red spot developed on the left shoulder which was very tender. Nov. 13, she menstruated; at this time the blood pressure was 170 systolic and 120 diastolic; she also complained of pain in the eyes. Nov. 22 a soft systolic murmur developed at the apex. She gradually became more restless, talkative, at times delirious, and was not influenced by bromides or codein. The temperature during the course of the disease ran from 98 to 104.2 F.; the pulse rate from 60 to 160, and respiration from 18 to 46. The striking symptoms were rigidity of the neck, severe pain in the head, neck, shoulders and abdomen, irrationality, unconsciousness, restlessness and frequent involuntary micturition and defecation. In addition, there were muscular twitchings, knotting of the muscles and strabismus of the right eye. The blood pressure was 150 systolic, 130 diastolic, hemoglobin 80 to 90%. The pulse was dicrotic, frequently weak and irregular and at times there were Cheyne-Stokes respirations. Pressure on the back of the neck caused dizziness. Dec. 16 her pulse was 120, temperature 99.6 per rectum; she was very sore all over; vomiting frequent; there was slight ankle-clonus of both legs; the knee-jerks were absent or very faint. At one time there was paralysis of the left external rectus and slight involvement of the muscles of the face and right side. Subsequently (Dec. 16) movements of the left eye were normal and the facial muscles nearly so, but there was complete paralysis of the right external rectus. The blood pressure was 140 systolic and 120 diastolic; the mind was fairly clear, with occasional delirium and involuntary urination; marked leukocytosis, with a high eosinophilia, was present.

Dec. 21, at 1:30 p. m., the patient became rigid with slight convulsive twitchings of the muscles after a paroxysm of pain in the head, neck, right arm and shoulders. The head was bowed back, jerking; then she would bury it in the pillow. She became unconscious following a chill. At this time the temperature was 104, the pulse rate 160. Dec. 22 another paroxysm of pain came on, but this time without convulsive twitching of the muscles. At 4:45 a. m. the following day another paroxysm of pain came on, and this time the patient rolled from side to side in bed. At 6:30 a. m. on the same day these paroxysms of pain became more frequent and of longer duration, and at this time the patient cried out with extreme pain in the head, twitching of the muscles, followed by a short chill; just before the chill she became unconscious. Such paroxysms became more frequent, and Dec. 26 they were so severe that the muscles all over the body twitched, throwing her legs from

one side of the bed to another. Dec. 27, at 8:45 a. m., she turned over on the left side with the head and feet thrown back for one-half minute; this was followed by 8 minutes of muscular twitchings and trembling of the lower extremities; death occurred on the same day.

NECROPSY (Dr. E. R. LeCount): Outside of the central nervous system no appreciable change was noticed in any organ that might be ascribed to botulismus, and therefore only the anatomic diagnosis is given here: Fibrino-

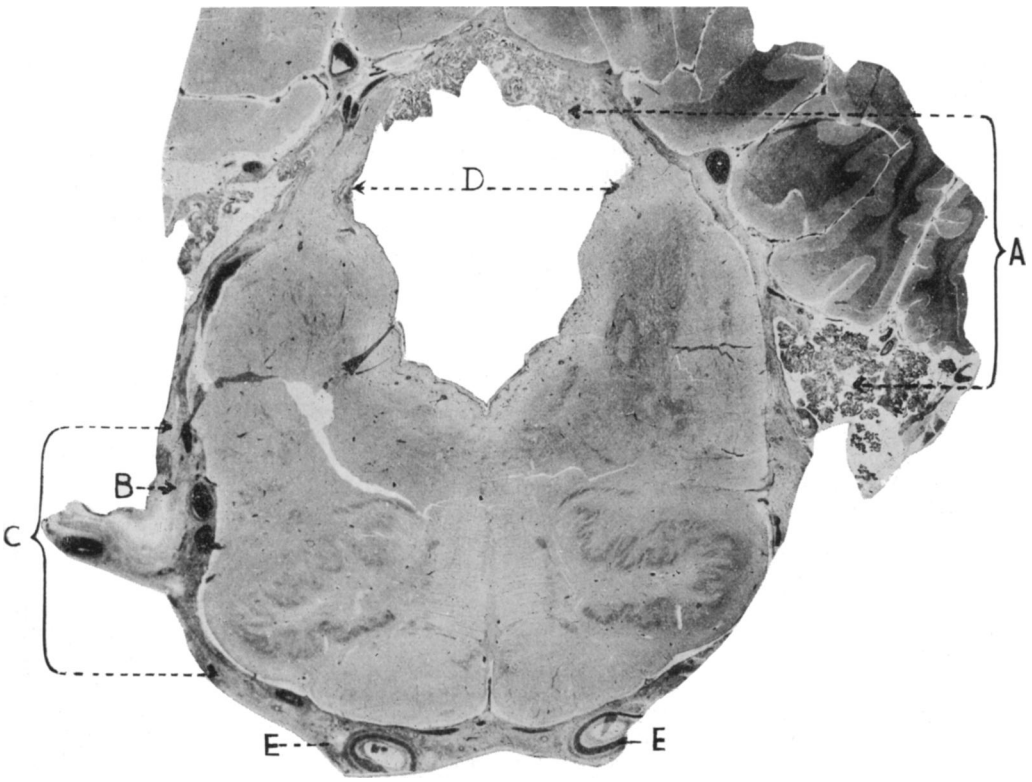

Fig. 1.—Camera lucida; photomicrograph; X 5. Section through middle of olives. A, plexus chorioideus densely infiltrated with lymphocytes; B, NN. facialis and acusticus free of infiltration; C, densely infiltrated and thickened pia-arachnoid; D, lymphocytic infiltration of subependymal layer; E, endarteritis in vertebral arteries (recently organized thrombus).

purulent basilar leptomeningitis; marked edema and anemia of the brain; anemia of the leptomeninges; foramen-magnum-pressure-furrow of the cerebellum; moderate internal hydrocephalus; marked general anemia; cloudy swelling of the liver and kidneys; fatty changes of the liver; hypostatic hyperemia of the stomach, urinary bladder and duodenal mucosa; moderately

distended bladder; slight hyperplasia of the biliary lymph glands and of the thyroid gland; left fibrous pleuritis; fibrous adhesion between the mesosigmoid and left ovary; localized hyperemia of the back (beginning pressure necrosis); moderate general obesity; accessory furrow of the under surface of the right lobe of the liver; fat replacement of the axillary lymph glands.

The calvarium is easily removed. In the longitudinal sinus there is a little fluid blood. There is practically no space between the two layers of the arachnoid. The outside of the cerebellum is rather dry. The cerebral veins are flat and mostly empty, both in front and behind. There is a slight but definite gray, purulent exudate covering the basilar and vertebral arteries. The ventricles of the brain are full of fluid. The region behind the chiasma

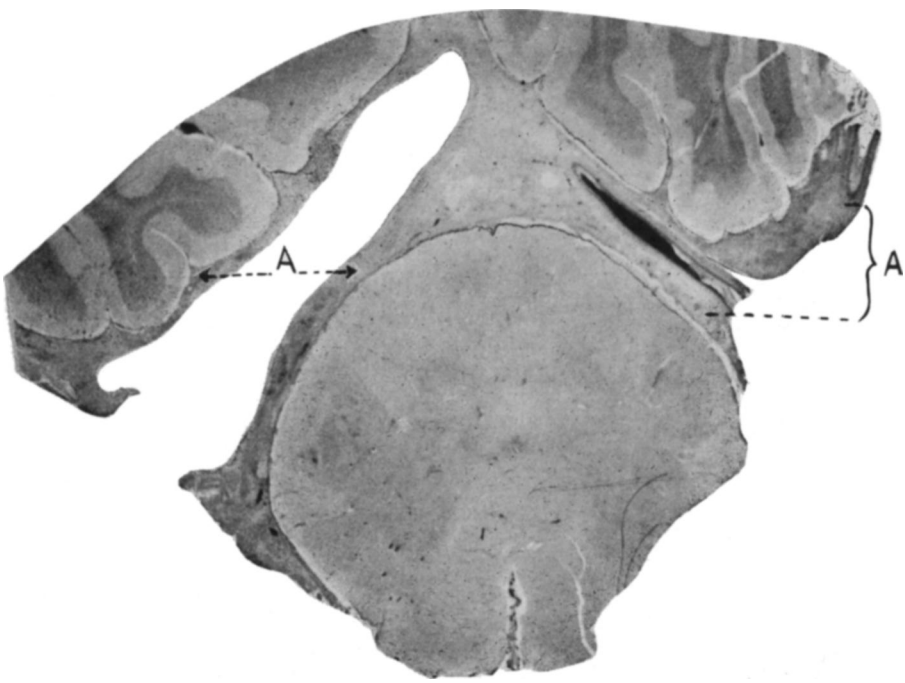

Fig. 2.—Camera lucida; photomicrograph; X 5. Section of medulla at decussation of pyramids. A, densely infiltrated and thickened pia-arachnoid.

bulges as though the third ventricle was full of fluid, and the tissue limiting this fluid on the bottom of the brain is translucent. The under surface of the temporal and occipital lobes is flat and semifluctuant from fluid in the ventricles. There is an exudate filling the tissue behind the medulla and in the region of the cisterna. In the substance of the cerebellum there is no change except that the vessels are rather bloodless. The lining of the left lateral ventricle is smooth and wet, and the ventricle is a little enlarged, the brain tissue about it soft. In the posterior horn of this ventricle the lining is greenish from exudate. The cerebrospinal fluid is distinctly turbid. The condition in the left hemisphere and ventricle is similar to that of the right. The substance of the cerebrum is watery and soft; the blood vessels empty. There is

no focal lesion in the brain. In the sinuses of the back of the dura there is only fluid blood. There is a brown fluid in the middle ear; the membrane here is intact. There is gray mucus in the sphenoid sinus with a thin, pink fluid, and a similar fluid in the ethmoid and frontal sinuses. There is no gross change in the hypophysis except that the substance is wet.

The whole brain-stem with the medulla, the pons, a portion of the cerebellum and spinal cord, was removed, sectioned serially and stained by the Weigert-Pal method, eosin-hematoxylin, phosphotungstic-acid-hematoxylin, and Nissl stains, as well as by stains to demonstrate bacteria. Sections were also taken from the central nuclei.

In sections stained by the Weigert-Pal method there is no change in the myelin sheaths. The fibers stand out sharply against the gray matter throughout. The eosin-hematoxylin stain reveals the changes best. They consist of a dense lymphocytic infiltration of the bulbospinal pia-arachnoid, the subepen-

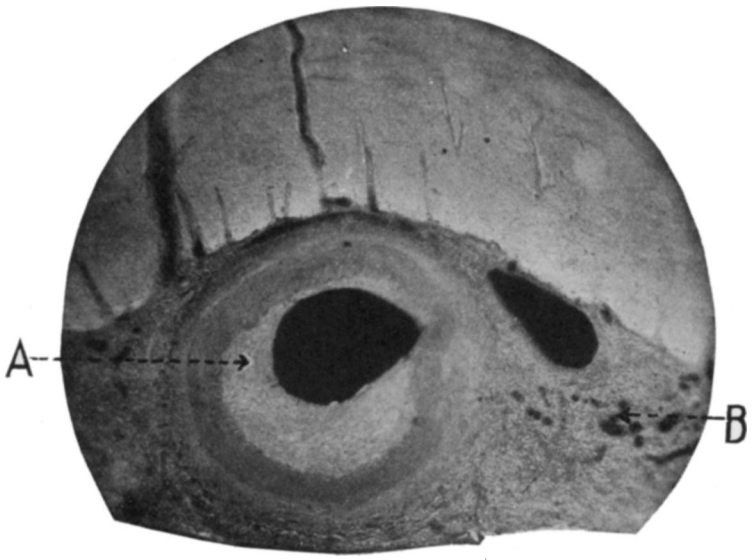

Fig. 3.—Photomicrograph; X 30. A, endarteritis of basilar artery; B, densely infiltrated and vascular pia-arachnoid.

dymal layer, the tela choroidea, tegmentum and choroid plexus (Fig. 1). At the lowest level of the olives and about the spinal cord the leptomeninges are four times the normal thickness (Fig. 2). The infiltration in the pia-arachnoid, profuse throughout, is especially dense about its blood vessels, both arteries and veins. About the capillaries and arterioles of the floor of the fourth ventricle and aqueduct of Sylvius, they form dark specks, easily seen with a hand-lens, 3 diam. (Fig. 1). The lumen of the basilar and vertebral arteries is partly obliterated by a circular bundle of long, spindle-shaped cells with elongated, dark-staining nuclei, recently organized granulation tissue forming a circular bundle of from 20 to 30 cell-layers, closely attached to the internal elastic membrane (Fig. 3). This endarterial thickening is readily followed through the whole length of the vertebral arteries and the basilar artery, obliterating from one third to one half of their lumen, and a similar thicken-

ing of the intima can be followed in at least three of the medium sized branches. Most of the smaller arteries and arterioles are filled with lymphocytes and some desquamated endothelial cells, but in a few arterioles the endothelial leukocytes predominate. The walls of all the vessels are infiltrated with lymphocytes which also fill the perivascular space; veins and arteries are equally involved. In the veins and arterioles all the coats are uniformly affected, whereas in the larger arteries the media is comparatively free of inflammatory changes and lymphocytic infiltration. The acoustic area is densely infiltrated, the lymphocytes in that region pervading the central gray matter. All the minute arterioles along the raphé are almost obliterated by lymphocytes, but other vessels in the substance of the medulla and brain-stem have hardly a sprinkling of lymphocytes in or about them, and the majority are entirely free

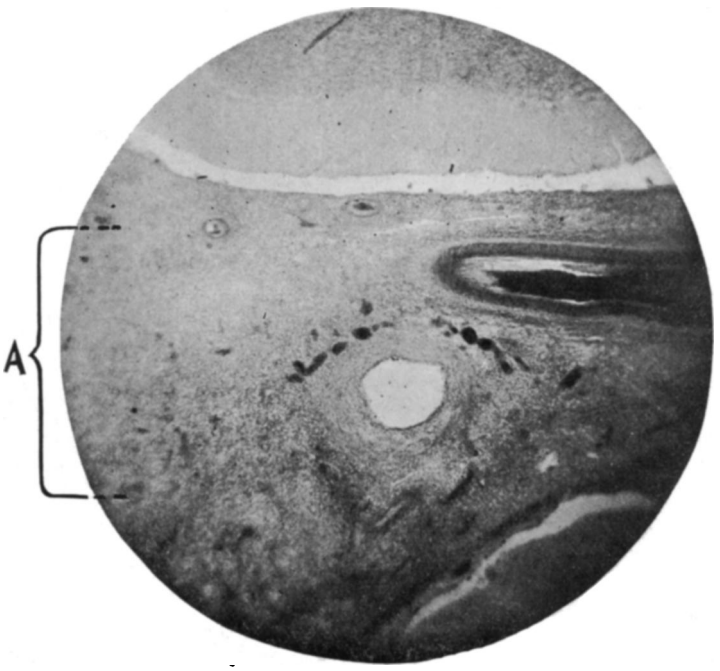

Fig. 4.—Photomicrograph; X 30. A, tegmentum markedly infiltrated with lymphocytes.

from such alterations. The ventral pia-arachnoid, especially in the neighborhood of the basilar and vertebral arteries, is extremely vascular (Fig. 3). A mass of capillaries with projecting protoplasmic buds are seen, irregular in size and shape, some of them communicating with each other and giving the appearance of granulation tissue. The infiltration in this region is profuse, the lymphocytes being closely packed between the capillaries. In sections taken, at the postmortem examination, from the lining of the ventricle where there was so much exudate, in places greenish, there is a great deal of edema and the greater portion, about 2 cm. by 4 mm., is fenestrated from necrosis and the cells are scanty. In places there is only a fibrillar network with scattered glia-cells and nuclear material. This necrotic region involves both the white and gray matter (Fig. 5). All the vessels in the subependymal layer are densely

infiltrated with lymphocytes and to a lesser degree with plasma cells and endothelial leukocytes. This infiltration also fills the spaces about these vessels and has also invaded considerably the surrounding subependymal tissue (Fig. 5). The veins are filled with erythrocytes, while the arteries are empty as a rule. The lumen of most of the small arterioles is densely packed with lymphocytes. In the center of two veins are masses of fibrin. The larger ganglion cells in the non-necrosed region stain deeply; they have swollen and pale nuclei, bulging in many instances at the periphery of the cell.

The larger neurons of the medulla, pons and cerebellum are normal; the Purkinje cells with their Nissl granules are unaltered. The folds of the pia-arachnoid, which dip into the cerebellar fissures, are also densely infiltrated with lymphocytes and contain engorged veins. Careful examination of the

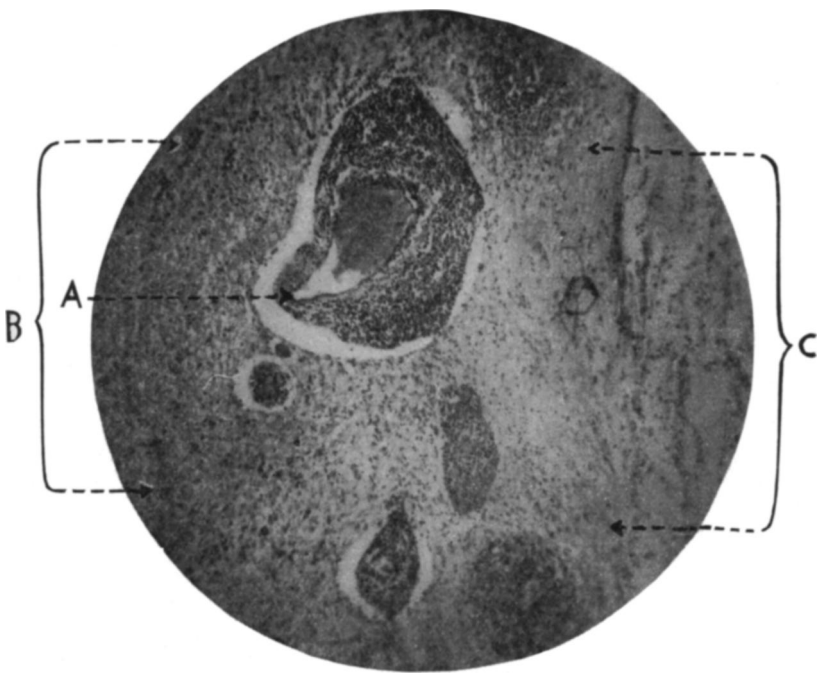

Fig. 5.—Photomicrograph; X 65. A, marked perivascular lymphocytic infiltration; B, dense lymphocytic infiltration of subependymal layer; C, region of extensive ischemic necrosis.

cells of origin of the cranial nerves does not reveal any characteristic change. The cell-bodies are uniformly swollen, with pale-staining, large nuclei and distinctly staining nucleoli. Only the uppermost cells, those nearest the ependyma, of the occulomotor and trochlear niduli, in the immediate neighborhood of some densely infiltrated vessels, are irregular in shape, the Nissl granules faint or invisible, and of some of the ganglion-cells only a faint outline can be distinguished. Here the lymphocytic infiltration is not only about the vessels, but also diffused in the central gray substance and the tegmentum at the decussation of the trochlear nerve. In the section through the distal end of the nucleus ambiguus, the edema in the medulla is more pronounced, the

pia thicker and more densely infiltrated with lymphocytes. The aqueduct of Sylvius is distended, and its ependymal lining as well as that of the 4th ventricle is somewhat desquamated, especially from the floor. The pia arachnoid of the cervical portion of the spinal cord is thick and densely infiltrated with lymphocytes and also a considerable number of plasma cells. The spinal cord and its vessels are free from lymphocytes, except the end arterioles along the ventral and dorsal fissures, which are also densely infiltrated and their lumen almost entirely obliterated by lymphocytes. The cranial and spinal nerves are not involved in the infiltration; the nerve-trunks can be clearly seen traversing the meninges with hardly any infiltration about them.

A careful examination of sections of the heart, lungs, liver, spleen, pancreas, kidneys and lymph glands was also made; they were quite free of disease; none of the arterioles show any thickening of the intima and in many of these sections there are small arteries comparable in size with those in the brain-stem where the recently organized thrombi obliterate the channels in part.

Histologic Anatomic Diagnosis: Subacute bulbospinal meningitis, choroiditis and ependymitis; endarteritis (recently organized thrombi) of the basilar and vertebral arteries and their branches; edema of the brain and the leptomeninges; internal hydrocephalus; slight ischemic necrosis and pressure atrophy in the motor cells of origin of the cranial nerves; marked ischemic necrosis about the third ventricle; thrombosis of ependymal veins.

Bacteriologic Examination (Dr. S. J. House): At the postmortem examination material from the exudate at the base of the brain and in the ventricles was put into 4 blood-serum slants; cover-glass preparations from these revealed no bacteriae; on blood-agar plates incubation with material of these 4 tubes yielded no growth; moreover, in these tubes after 7 days at 37 C. no growth developed. Material of these 4 tubes was also transferred to medium maintained for 5 days at 37 C. and 2 days at room temperature under anaerobic condition; no growth developed. Efforts to obtain growth from the spleen under both aerobic and anaerobic conditions were negative.

Although several weeks had elapsed since the outbreak and considerable of the ham and salted pork had been thrown away or otherwise disposed of, cultures were made from a number of places of what remained with negative results.

In microscopic preparations from a number of skeletal muscles and brain tissue taken at the necropsy, no bacteria were found.

Animals were inoculated with pieces of the pork taken from several places, but no deleterious effects were observed. Not only was a prolonged search made for trichinella in the pork and ham which remained in the barrel, but also in such places as the diaphragm, laryngeal muscles and other muscles of the body of the patient; none was found.

DISCUSSION

Taking into consideration the illness in several persons after partaking of the same food, the similarity of the clinical course and symptoms and their correspondence with the changes in the central nervous system, the exclusion of trichinosis, the absence of the symptoms of ptomaine poisoning, especially of bowel disturbances, also the fact that the alterations in the brain-stem do not correspond to syphilis, epidemic encephalitis or to other known forms of disease, as well as

that they do resemble what is at present known in regard to the changes produced by botulismus, the conclusion seems justifiable that the illness in at least four of the persons mentioned was due to botulismus.

It is well established that the contamination of food with B. botulinus may be rather widely disseminated,[8] and unless such scattered foci in the food are examined or used for animal experiments, the nature of the contamination may not be ascertained.

There are reports [9] of the recovery of B. botulinus from the human spleen; on the other hand, failure to obtain the organism from the organs of animals experimentally inoculated are also recorded.[10]

The pathologic changes in the central nervous system of animals have been described in many instances. Minute disseminated hemorrhages in the brain-stem and medulla, especially in the floor of the fourth ventricle, with degenerative changes in the ganglion cells of origin of the motor cranial nerves, have been reported by Van Ermengem;[3] Roemer and Stein [11] and Marinesco.[12] Kempner and Pollack [13] found numerous hemorrhages in the anterior horn of the spinal cord. Intra- and peri-vascular lymphocytic infiltration has been noted by Ossipoff.[14] In most of these reports emphasis is laid on the degenerative changes in the ganglion cells of origin of the cranial nerves or in the anterior horn of the spinal cord. Graham and Bruckner [10] found a meningitis grossly during an epidemic in horses, B. botulinus being recovered from the ensillage which had served as food.

Reports on the changes in man vary to a certain extent. Brownlie [15] found a basal meningitis with hyperemia of the brain and spinal cord as the only change in one case (microscopic examination not reported). Concerning the material sent by Fischer [16] to the Pathologic Institute at Giessen (7 cases, 6 deaths), the report stated that no characteristic changes were found. In the examination made by Kellert and Nevin,[6] the pia at the base of the brain was thick and opaque; a few lympho-

[8] Schlossberger: Arch. Pathol. Anat., 1854, 11, p. 569. Kaatzer: Deutsch. med. Wchnschr., 1881, 7, p. 73. Seyler, Hoppe (cited by Eulenburg): Realencyclop. d. gesamm. Heilk., 1890, 21, p. 369.

[9] Van Ermengem, Schuhmacher, Burger, Landmann (cited by Schede, footnote 7).

[10] Graham and Bruckner: Jour. Bacteriol., 1919, 4, p. 1.

[11] Arch. f. Ophth., 1897, 5, p. 43.

[12] Presse Med., 1897, 5, p. 41.

[13] Deutsch. med. Wchnschr., 1897, 23, p. 505.

[14] Ann de l'Inst. Pasteur, 1904, 58, p. 297.

[15] Brit. Med. Jour., 1918, 1, p. 617.

[16] Ztschr. f. klin. Med., 1916, 59, p. 58.

cytes were present in the anterior horn of the spinal cord and shrunken ganglion cells with swollen nucleus. Burger,[17] who made several post-mortem examinations, mentions changes in one brain; these consisted in dust-like desintegration of the Nissl granules and excentric position of nuclei, in the ganglion cells of origin of the oculomotorius. Paulus [18] described the changes in one brain; he found numerous foci of hemorrhage in the medulla and basal nuclei, especially at the floor of the fourth ventricle; there was no round cell infiltration or any sign of inflammation. The only reports I have found dwelling at any length on the microscopic changes are by Ophüls [19] and Dickson,[20] who both found perivascular hemorrhages and thrombosis of the arteries and veins in the brain and leptomeninges. In their instances the illness had lasted from 3 to 13 days. The longer duration of the illness, 6 weeks in the case here reported, may account for the more marked cellular exudate in the leptomeninges, as well as for the partial obliteration of the arteries.

Dickson's extensive experiments on 30 guinea-pigs, 37 rabbits, 30 cats and 4 dogs further convinced him that the pathognomonic change in botulismus is thrombosis secondary to some alteration of the intima, in man as well as in animals.

CONCLUSIONS

Bacillus botulinus produces a poison which is highly toxic to man and animal.

The changes are confined to the vascular system. Thrombosis in arteries and veins is the initial change followed by ischemic necrosis and later by inflammation.

The poison has no direct action on the nerve cells; the retrogressive changes are secondary and due to the disturbed blood supply.

The ganglion cells of origin of the motor cranial nerves are always involved because their blood supply is derived from terminals of branches of the vertebral arteries which seem to be the seat of predilection of the thrombosis.

[17] Med. Klin., 1913, 9, p. 1846.
[18] Jour. f. Psychol. u. Neurol., 1915, 21, p. 201.
[19] Arch. of Int. Med., 1914, 14, p. 589.
[20] Rockefeller Inst. f. Med. Res., 1918; Monograph, p. 117.